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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Toni-Junell Herbert
Reed Smith LLP
3110 Fairview Park Drive
Suite 1400
Falls Church, VA 22042

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,911	FOCKE ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9,14-24 and 28-33* is/are pending in the application.

4a) Of the above claim(s) *14-24 and 28-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the examiner of record for your application has changed. To aid in paper matching, please address all future correspondence to Michael Szperka, Art Unit 1644, Technology Center 1600.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2006 has been entered.

Claim 1 has been amended.
Claims 5, 7, 8, 10-13, 25-27 have been canceled.
Claims 1-4, 6, 9, and 14-24, 28-33 are pending.
Claims 14-24 and 28-33 stand withdrawn for the reasons of record as being drawn to non-elected inventions.

Claims 1-4, 6, and 9 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

2. The rejection of claims 3 under 35 USC 112, second paragraph has been withdrawn in light of applicant's persuasive arguments that the recitation of "at least 5 consecutive solvent-exposed amino acids" does further limit the claimed genus of peptides in pharmaceutical compositions as is currently recited in the independent claim. The rejection of claim 7 is rendered moot by applicant's cancellation of said claim in the amendments submitted February 1, 2006.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 7, and 9 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ferreira et al. (FASEB J, 1998, 12:231-242, of record, see entire document) as evidenced by Gajhede et al. (of record as reference AD1 on the ISD received 6/20/02, see entire document).

Ferreira et al. teach pharmaceutical compositions comprising birch pollen allergen Bet v 1 variants. These variants include 6 polypeptides which each comprise a single point mutation from a Bet v 1 sequence, as well as a polypeptide that comprises all 6 of the individual mutations (see particularly Figure 1 and the paragraph spanning pages 235 and 236). The sequence of the polypeptides disclosed by Ferreira et al. comprise at least 5 consecutive solvent exposed amino acids as evidenced by the solvent accessibility data presented in Figure 2A of Gajhede et al. and the solvent exposed amino acids appear on the surface of the protein within an approximately 500 square angstrom patch based upon the NMR and crystallographic structure data presented by Gajhede et al.

Applicant has argued that Ferreira et al. teaches the use of six-point mutants of Bet v 1 while the instant claims are limited to single point mutations. The second sentence of page 9 of the reply submitted February 1, 2006 states "Similarly, the mutant Bet v 1 a (A1) is a six point

mutant which differs from Bet v 1 a itself by a single point mutation in position number 30." The examiner is confused by applicant's arguments because it is unclear how a sequence that differs from another sequence by a single point mutation can comprise six mutations, and as such this argument is not convincing.

Applicant also argues that Ferreira et al. do not teach mutants having 15-19 amino acid residues. It does appear that Ferreira et al. do not teach the use of fragments of their Bet v 1 single-point or six-point mutants, but they do teach the use of Bet v 1 peptides (see particularly the paragraph spanning pages 233 and 234 and the text of Ebner et al., J. Immunol. 1993, 150:1047-1054, see entire document, the reference cited by Ferreira et al. as the source of their Bet v 1 peptides. Note that the right column of page 1049 of Ebner indicates that 75 peptides were made as docecapeptides which overlap by 10 amino acids. As such, peptides per se are taught. Further, independent claim 1 recites that the peptide "has a length of 8 to 50 amino acids". The term "has" is equivalent to the term "comprising" when referring to biological sequences. "Comprising" allows for the addition of an unspecified biological sequence to either end of the recited sequence, and thus the instant claim recitation merely establishes a lower limit for the length of the claimed polypeptide (8 amino acids) but does not establish an upper size limit. Given that the polypeptides of Ferreira et al. are larger than 8 amino acids, they meet the limitation of the claims.

Applicant's final argument is that Ferreira et al. does not teach Bet v 1 mutant surface exposed peptides for the focusing of IgG antibodies. Applicant is reminded that the instant claims recite a product, and the recitation that upon administration the claimed product leads to the production of protective IgG antibodies provides a functional property of the product. The functional property of inducing a protective IgG response is an inherent property of the administered amino acid sequence. Such a recitation is not accorded patentable weight unless the structure required to meet such a recitation imposes structural requirements upon the sequence of the peptide present in the composition. The specification does not appear to teach what structures are required for the induction of protective IgG antibodies and since the polypeptides taught by Ferreira et al. meet the recited structural limitations of the claims the polypeptides of Ferreira et al. comprise the recited functional properties as well.

Therefore, the rejection is maintained.

The following are new grounds of rejection:

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6, and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a broad genus of compositions comprising peptides wherein the peptide is identical to birch pollen allergen Bet v 1 at all positions except one. To support such a genus applicant has provided the peptides of SEQ ID NOs:1-6. The disclosure of these peptides does not indicate that applicant was in possession of the claimed invention for the following reasons:

The independent claim recites that the peptide is identical to birch pollen Bet v 1 at all positions except one, but the specification does not provide a full length Bet v 1 polypeptide sequence. Many Bet v 1 sequences are known in the art, and many of them differ from each other at only one amino acid (Friedl-Hajek et al., Molecular Immunology, 1999, 36:639-645, see entire document particularly Figure 1, and Swoboda et al. J. Biol. Chem. 1995, 270:2607-2613, see entire document particularly Figure 1). Without reference to a particular Bet v 1 sequence it cannot be known if a peptide is identical to a birch pollen allergen Bet v 1 at all positions except one because there is no basis on which to make the comparison. Indeed, a comparison of SEQ ID NO:1 to the numerous Bet v 1 sequences disclosed in Friedl-Hajek et al. and Swoboda et al. indicates that SEQ ID NO:1 of the instant application contains more than one amino acid difference to a birch pollen allergen Bet v 1 sequence depending on what Bet v 1 sequence is

used as the recited allergenic protein. Note that this is also true of comparisons between applicant's SEQ ID NOs:2-6 with the multitude of known Bet v 1 sequences.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Applicant has recited structural features including solvent exposure in the independent claim and the presence of solvent exposed amino acids in a 500 square angstrom patch in dependent claim 2, and the specification teaches that the structure of Bet v 1 is known in the art and can be used to identify peptides that have these structural properties (see particularly the last paragraph of page 3 and page 9 of the specification). These structural features do not help in the resolution of the above discussed limitation concerning identity with a Bet v 1 allergen at all positions except one.

The functional property applicant has recited is that the claimed peptide when administered elicits the production of a protective IgG response. The specification discloses that when the peptides of SEQ ID NOs:1-6 were administered to human birch pollen allergic patients as part of skin prick testing no allergenic activity could be detected (see particularly pages 15-17 of the specification) yet these same polypeptides could induce IgG antibodies in mice and rabbits that bound to full length Bet v 1 allergen (see particularly pages 18-21) and competed with IgE from birch pollen allergic human patients for binding to the full length Bet v 1 allergen. The structure of the peptide required to provide the functional properties of not being bound by IgE from birch pollen allergic patients (a property not currently recited) but that does elicit an IgG response that binds the full length Bet v 1 allergen is not readily apparent in that the specification does not appear to disclose what structure or amino acid sequence is required to give rise to these functional properties and therefore must be present in the genus of claimed peptides. It is known

in the art that even single amino acid changes can completely disrupt the binding between an antibody and an antigen (Colman, P.M., Research in Immunology, 1994, 145:33-36, see entire document, particularly the paragraph that starts in the right column of page 33) and the breadth of the claims read on peptides that comprise single amino acid changes. Given that single amino acid changes can completely abrogate antibody-antigen binding, it is not clear what structure is required of the administered peptide of the instant invention such that it has the ability to elicit an antibody response that binds the full length native Bet v 1 allergen.

In light of all of the above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus pharmaceutical compositions comprising peptides that differ from birch pollen allergen Bet v 1 at only one position and that are capable of producing a protective IgG antibody response upon administration to an individual and that the disclosure fails to adequately disclose what would be required for a peptide in a pharmaceutical composition to be recognized by a skilled artisan as a peptide that differs from birch pollen allergen Bet v 1 at only one position and is capable of producing a protective IgG antibody response upon administration to an individual. Thus, Applicant was not in possession of the claimed genus pharmaceutical compositions comprising peptides.

7. Claims 1-4, 6, and 9 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions comprising peptides wherein the peptides contain a single point mutation in comparison to the sequence found in birch pollen allergen Bet v 1, comprise a number of solvent exposed amino acids, and lead to the production of a protective IgG response upon administration. The specification discloses on page 9 that the structure of Bet v 1 is known and that reference can be made to this structure to identify solvent-exposed amino acids. The specification also discloses the peptides of SEQ ID NOs:1-6 which were made by adding a cysteine residue to either the C or N-terminal of Bet v 1 peptides, and that the peptides of SEQ ID NOs:1-6 could not be bound by IgE from birch pollen allergic

patient but could elicit an IgG response in mice and rabbits that competed with the IgE from birch pollen allergic patients for binding to the full length Bet v 1 allergen (see particularly pages 12-25).

Applicant's claimed compositions are broader than those comprising the peptides of SEQ ID NOs:1-6 in that the one amino acid difference between the claimed peptide and a Bet v 1 sequence can be located anywhere within the peptide excepting dependent claim 6 which limits the location of the non-identical amino acid to either the N-or C-terminal of the claimed peptide. However, the specification does not disclose a full length sequence of Bet v 1 that is to be used in making the determination if a peptide differs from Bet v 1 at only one position. Numerous sequences of Bet v 1 are known in the art (Friedl-Hajek et al., Molecular Immunology, 1999, 36:639-645, see entire document particularly Figure 1, and Swoboda et al. J. Biol. Chem. 1995, 270:2607-2613, see entire document particularly Figure 1). Without a reference Bet v 1 sequence, a skilled artisan would not know if compositions comprising a peptide of particular sequence differed from Bet v 1 at one, multiple, or no amino acid positions, and as such a skilled artisan would be unable to make compositions that would be know to be encompassed by applicant's claims.

Applicant has also recited that the claimed compositions produce protective IgG responses upon administration. The specification defines protective IgG antibodies on page 5 of the specification, teaching that protective antibodies prevent IgE antibodies from binding to the allergenic protein. This definition appears to indicate that the protective IgG antibodies prevent the binding of all IgE antibodies that specifically bind that allergen. The specification does not appear to teach what changes can or cannot be made to a Bet v 1 peptide such that it comprises these functional properties and meets the structural limitations of the claims. As such it appears that a skilled artisan would not have any expectation of success that when a peptide was made that met the recited structural limitation that it would also comprise the requisite functional properties. The data presented in Example 4 and Table 6 of the specification indicate that the IgG antibodies elicited by the peptides of SEQ ID NOs:1-6 could compete with IgE antibodies for binding to some but not all epitopes recognized by IgE found in birch pollen allergic patients. Table 6 demonstrates that while IgE binding to full length Bet v 1 allergen was reduced, it was not eliminated and thus prevented under any experimental condition, and in some instances the

presence of IgG antibodies generated by immunization with the peptides of SEQ ID NOs:1-6 did not alter allergen-specific IgE binding at all. As such, the examples of the specification do not teach any peptide that produces a protective IgG response concordant with the definition of that term on page 5 of the specification.

Further, it is known in the art that even single amino acid changes can completely disrupt the binding between an antibody and an antigen (Colman, P.M., Research in Immunology, 1994, 145:33-36, see entire document, particularly the paragraph that starts in the right column of page 33) and the breadth of the claims read on peptides that comprise single amino acid changes. Given that single amino acid changes can completely abrogate antibody-antigen binding, it is not clear what structure is required of the administered peptide of the instant invention such that it has the ability to elicit an antibody response that binds the full length native Bet v 1 allergen.

Therefore, based upon the breadth of the claims, the difficulty in making a peptide that differs from Bet v 1 at only one amino acid position without reference to a particular Bet v 1 sequence given the large number of different sequences that are known, the difficulty in identifying what sequence or structure is required of an administered peptide such that it can produce a protective IgG response and the lack of guidance or working examples concerning peptides that produce a protective IgG response that prevents the binding of all Bet v 1 allergen-specific IgE to the full length Bet v 1 allergen, a skilled artisan would be unable to make and use the claimed invention without conducting undue research.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-4, 6, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the metes and bounds of the claimed subject matter is unclear because given the large number of Bet v 1 sequences known in the art as evidenced by Friedl-Hajek et al. (Molecular Immunology, 1999, 36:639-645, see entire document particularly Figure 1) and Swoboda et al. (J. Biol. Chem. 1995, 270:2607-2613, see entire document particularly Figure 1), and the lack of a recited Bet v 1 reference sequence, a

skilled artisan would not know if a given peptide is encompassed by the claimed subject matter. This is because said peptide may differ by one amino acid from Bet v 1 sequence X, differ by 3 amino acids from Bet v 1 sequence Y, and yet be identical to Bet v 1 sequence Z. Since a skilled artisan cannot clearly identify what peptides are or are not encompassed by the claimed invention, the instant claims are indefinite.

Claim Rejections - 35 USC § 102

10. Claims 1-4, 7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Vik et al. (Int Arch Allergy Immunol, 1993, 101:89-94, see entire document) as evidenced by Gajhede et al. (of record as reference AD1 on the IDS received 6/20/02, see entire document), as evidenced by Friedl-Hajek et al. (Molecular Immunology, 1999, 639-645, see entire document), and as evidenced by Mandler et al. (J. Immunol. 1993, 150:407-418, see entire document).

Vik et al. teach peptides derived from the amino terminal of Bet v 1 and their use in pharmaceutical compositions. One of these peptides, Bet v I 23-38, is taught as being coupled to the adjuvant BSA, and this peptide both in its free and BSA-coupled forms were administered to patients for skin prick and nasal provocation tests (see particularly the left column of page 90, the paragraph spanning pages 91 and 92, and the left column of page 92. The sequence of the administered Bet v I 23-38 peptide is provided in Figure 1, and it can be seen that this peptide differs from many birch pollen allergen Bet v 1 sequences at position 30 (using the numbering scheme of Figure 1 of Vik et al.) since the peptide of Vik et al. contains a phenylalanine at this position while isoleucine and valine occur at this positions in other naturally occurring birch pollen allergen Bet v 1 sequences (see Friedl-Hajek et al., particularly Figure 1 on page 641). As such, the Bet v I 23-38 peptide of Vik et al. is identical to allergenic Bet v 1 sequences such as Bet v 1at5, Bet v 1at2, Bet v 1at76, Bet v 1d, Bet v 1at10, and Bet v 1at15 at all positions except one. Comparison of the Bet v I 23-38 peptide sequence of Vik et al. to the solvent-exposure chart of Bet v 1 amino acids disclosed by Gajhede et al. indicates that this sequence comprises at least 3 consecutive solvent-exposed amino acids, and the structural data also presented by Gajhede et al. also indicate that these residues appear within 500 square angstroms of each other on the surface of the Bet v 1 allergen. Vik et al. also teach that another peptide, Bet v I 1-16 had

activity similar to Bet v I 23-38 in their model system (see particularly the paragraph spanning pages 92 and 93). The Bet v I 1-16 peptide comprises at least five N-terminal amino acids, is very solvent-exposed as per the data of Gajhede et al., and since numerous naturally occurring sequence variations occur in this region of Bet v 1 as shown by Friedl-Hajek it will vary by one amino acid from some Bet v 1 allergen sequence.

It is noted that Vik et al. do not teach that their peptides upon administration produce a protective IgG response. The specification teaches on page 5 of the specification that "[P]rotective antibodies ... prevent IgE from binding to the respective allergenic protein from which the [immunizing] peptides are derived." It is well known in that art that administration of a foreign antigen leads to an antibody response, and it is also known that production of IgE by B cells primarily occurs from cell previously committed to producing IgG1 (Mandler et al., see entire document, particularly the abstract). The process by which antibodies switch their isotype does not alter antigen specificity, and as such the IgG antibodies that are elicited first will have the same antigen specificity as the later IgE antibodies. Therefore, the earlier produced IgG antibodies will compete with IgE for binding to the target antigen thus making them blocking or protective antigens as per the definition provided in the specification. It is noteworthy that the peptides of Vik et al. are disclosed as comprising antibody epitopes, particularly IgE epitopes (see entire document, particularly the abstract).

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vik et al. (Int Arch Allergy Immunol, 1993, 101:89-94, see entire document) as evidenced by Gajhede et al. (of record as reference AD1 on the ISD received 6/20/02, see entire document), as evidenced by Friedl-Hajek et al. (Molecular Immunology, 1999, 639-645, see entire document), and as evidenced by Mandler et al. (J. Immunol. 1993, 150:407-418, see entire document) in view of Harlow et al. (Antibodies, A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, pages 72-87, see entire document).

Vik et al. teach the multiple peptides from the amino terminal region the Bet v 1 allergen and detail the coupling of the Bet v I 23-38 peptide to BSA for use in pharmaceutical compositions (see entire document, particularly the abstract, Figure 1, and from the right column of page 91 to the right column of page 92). EDC was used to couple the peptide to BSA, and this strategy favors the formation of amide bonds between carboxylic acids and amines (Harlow et al., see entire document, particularly pages 84-85 and most particularly the first paragraph of page 84). Note that carboxylic acids are found on the two aspartic acids and the C-terminal of the Bet v I 23-38 peptide. The teachings of Vik differ from the instant claimed invention in that the Bet v I 23-38 peptide does not comprise one amino acid difference from some Bet v I sequences such as Bet v 1a (see particularly Figure 1 of Friedl-Hajek et al.).

Harlow et al. teach that peptide conjugation should be performed so that the coupled peptide is linked by its carboxyl- or amino terminal residue to the larger protein, and that sulfhydral coupling cysteines are useful for such purposes (see entire document, particularly the first paragraph of page 77). It is further taught that the easiest method to couple peptides is to add an extra amino acid on either the amino or carboxyl terminus to allow simple, one site coupling to the other protein, such as BSA, since methods that allow coupling to occur via internal or multiple residues should be avoided (see particularly the second paragraph of page 77).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add a cysteine to either the amino- or carboxyl-terminal of the Bet v I 23-38 peptide to allow for coupling to BSA. Motivation to do so comes from the fact that Vik et al. teach the peptide coupled to BSA using a strategy that couples the peptide to BSA at multiple sites, including internals sites, that Harlow et al. teach should be avoided when coupling peptides to larger proteins, and the fact that Harlow et al. teach that a simple method to ensure the coupling of a peptide to a larger protein at only one site is by introducing a cysteine at either the amino or carboxyl-terminal of the peptide. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success based upon the detailed protocols provided for coupling peptides provided by Harlow et al. (see particularly pages 82-83).

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
May 10, 2006

5/15/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER